Petition
PATENT PK1
Docket No. 273802801500
520
#26

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

Express Mail Label No.: EL329472716US Date of Deposit: May 21, 1999

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. § 1.10 on the date indicated above and is addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Kathy Johnston

Kathy Johnston

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Hagen et al.

Application No.: 06/810,002

Application Date: December 15, 1986

Patent No.: 4,784,950

Issued: November 15, 1988

For: EXPRESSION OF FACTOR VII ACTIVITY IN MAMMALIAN CELLS

TRANSMITTAL

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Enclosed please find the following:

- Application For Extension Of Patent Term Under 35 U.S.C. § 156 with Exhibits 1 through 9 (in duplicate)
- Check in the amount of $1,120.00
- Return Receipt Postcard

pa-379376

The Assistant Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16, 1.17, and 1.21 that may be required by this transmittal, or to credit any overpayment, to **Deposit Account No. 03-1952**.

Respectfully submitted,

Dated: May 21, 1999 By: _____

Nicholas S. Buffinger
Registration No. 39,124

Morrison & Foerster LLP
755 Page Mill Road
Palo Alto, California 94304-1018
Telephone: (650) 813-5816
Facsimile: (650) 494-0792

PATENT
Atty Ref. No. 273802801500

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. § 1.10 as Express Mail Label No. **EL329472716US** and is addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

May 21, 1999 Kathy Johnston
Kathy Johnston

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Hagen et al.

Application No.:	06/810,002
Application Date:	December 16, 1986
Patent No.:	4,784,950
Issued:	November 15, 1988
For:	EXPRESSION OF FACTOR VII ACTIVITY IN MAMMALIAN CELLS

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Commissioner for Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

Dear Sir:

In accordance with 35 U.S.C. § 156, Applicant, ZymoGenetics, Inc., a corporation of the State of Washington, having a place of business at 1201 Eastlake Avenue East, Seattle, Washington, 98102, (hereinafter "Applicant") represents that it is the assignee of the entire interest in and to Letters Patent of the United States No. 4,784,950, granted to Frederick S. Hagen, Mark J. Murray, Sharon J. Busby, Kathleen L. Berkner, Margaret Y. Insley, Richard G.

Woodbury, and Charles L. Gray for EXPRESSION OF FACTOR VII ACTIVITY IN MAMMALIAN CELLS by virtue of an assignment in favor of Applicant, recorded in the United States Patent and Trademark Office on March 14, 1986, at Reel 4533, Frames 482-486.

Applicant, through undersigned counsel, hereby applies for a 1,826 day (5 year) extension of the term of United States Patent No. 4,784,950 under 35 U.S.C. § 156 on the basis of the following information submitted in accordance with the provisions of Title 37 C.F.R. § 1.740(a) (1)-(17), set forth in the sequence of those subparagraphs. Filed herewith is a Certificate under 37 C.F.R. § 3.73(b) and a Power of Attorney authorizing the undersigned to file and prosecute this Application for Extension of Patent Term, and to transact all business in relations thereto (EXHIBIT 1).

(1) This application for extension is based upon the regulatory review period before the Federal Drug Administration (FDA) for the approved product, NOVOSEVEN®. NOVOSEVEN® contains recombinant human Factor VIIa (rhFVIIa), a recombinantly produced human coagulation factor. Letters of authorization executed by the marketing applicants to the patent assignee are attached as EXHIBIT 2.

NOVOSEVEN®, is a sterile, white lyophilized powder, containing the active ingredient rhFVIIa and the following inactive ingredients: sodium chloride, calcium chloride dihydrate, glycylglycine, polysorbate 80 and mannitol. NOVOSEVEN® is supplied in single use vials at one of two doses: 1.2 milligrams (mg) rFVIIa (60 KIU) or 4.8 mg rFVIIa (240 KIU). NOVOSEVEN® is reconstituted with Sterile Water for Injection, USP (not supplied with NOVOSEVEN®) to yield an injectable solution of 0.6 mg/milliliter (mL) rFVIIa at approximately pH 5.5 with 3 mg/mL sodium chloride, 1.5 mg/ml calcium chloride dihydrate, 1.3 mg/mL glycylglycine, 0.1 mg/mL polysorbate 80 and 30 mg/ml mannitol. NOVOSEVEN® is

approved for use in promoting hemostasis as further described in attached EXHIBIT 3 (which is the package insert for this product).

(2) The approved product was subject to regulatory review under Public Health Service Act, Section 351 (42 U.S.C. § 262).

(3) The approved product, "NOVOSEVEN®" (Biologics License No. 1261) received permission for commercial marketing or use after a regulatory review period under Public Health Service Act, Section 351 (42 U.S.C. § 262) on March 25, 1999.

(4) The active ingredient in NOVOSEVEN® is a recombinant form of human Factor VIIa (rhFVIIa). To the best of Applicant's knowledge, the permission for the commercial marketing or use of this product after such regulatory review period is the first permitted commercial marketing or use of such product under the Public Health Service Act.

(5) This Application for extension of patent term under 35 U.S.C. Section 156 is being submitted within the permitted 60 day period, which period will expire on May 25, 1999.

(6) The complete identification of the patent for which extension is being sought is as follows:

U.S. Patent No.: 4,784,950

Issue Date: November 15, 1988

Expires: November 15, 2005

Inventors: Frederick S. HAGEN, Mark J. MURRAY, Sharon J. BUSBY, Kathleen L. BERKNER, Margaret Y. INSLEY, Richard G. WOODBURY, and Charles L. GRAY

(7) A copy of the patent for which an extension is being sought, including the entire specification and claims, is attached as EXHIBIT 4.

(8) A receipt of maintenance fee payment has been issued with regard to U.S. Patent No. 4,784,950. A copy of the maintenance fee receipt is attached as EXHIBIT 5. A Certificate of Correction was requested, and was granted July 10, 1990, for U.S. Patent No. 4,787,950. A copy of the Certificate of Correction is attached as EXHIBIT 6. No disclaimer or reexamination certificate has been issued in connection with U.S. Patent No. 4,784,950.

(9) U.S. Patent No. 4,784,950, for which this extension is sought, generally claims DNA constructs encoding Factor VII, cells comprising the DNA constructs, and methods for making Factor VIIa. The active ingredient in the approved product, "NOVOSEVEN®", is a recombinant form of human Factor VIIa. The approved product is manufactured by recombinant

expression of a DNA construct encoding human Factor VII in a mammalian host cell, followed by isolation and activation of the recombinant product to produce human Factor VIIa.

Claims 24-32:

24. A method for producing a protein having biological activity for blood coagulation mediated by Factor VIIa, comprising:

establishing a mammalian host cell which contains a DNA construct comprising a DNA sequence encoding Factor VII;

growing said mammalian host cell in a an appropriate medium;

isolating the protein product encoded by said DNA construct produced by said mammalian host cell; and

activating said protein product to generate Factor VIIa.

The approved product is manufactured by recombinant expression of a DNA construct encoding human Factor VII in a mammalian host cell, followed by isolation and activation of the recombinant product to produce human Factor VIIa. Thus, this claim reads on the method for producing the approved product.

25. The method of claim 24, including amplification of the DNA sequence by cotransfection of the host cell with a gene encoding dihydrofolate reductase, wherein the appropriate medium comprises methotrexate.

The expression construct in the recombinant host cells used for the manufacture of the approved product has been amplified using the dihydrofolate reductase/methotrexate amplification system. Thus, this claim reads on the method for producing the approved product.

26. The method of claim 24 wherein said protein product is activated by reacting the protein with a proteolytic enzyme selected from the group consisting of Factor XIIa, Factor IXa, kallikrein, Factor Xa, and thrombin.

The proteolytic enzymes listed in this claim will activate Factor VII such as the recombinant human Factor VII produced in the claimed method, to form Factor VIIa. Thus, this claim reads on a method for producing the approved product.

27. The method of claim 24 wherein said DNA sequence comprises Factor VII cDNA.

The expression construct encoding Factor VII currently used for production of the approved product comprises cDNA sequence from human-derived cDNA. Thus, this claim reads on the method for producing the approved product.

28. The method of claim 24 wherein said DNA sequence comprises Factor VII genomic DNA.

Any DNA sequence encoding human Factor VII will encode the approved product. Thus, this claim reads on a method for producing the approved product.

29. The method of claim 24 wherein said DNA sequence comprises the cDNA sequence of FIG. 1b, from bp 36 to bp 1433.

The sequence of FIG. 1b, from bp 36 to bp 1433, encodes human Factor VII. Thus, this claim reads on a method for producing the approved product.

30. The method of claim 24 wherein said DNA sequence comprises the cDNA sequence of FIG. 1b, from bp 36 to bp 99, followed downstream by the sequence from bp 166 to bp 1433.

The expression construct encoding Factor VII currently used for production of the approved product comprises the sequence of FIG. 1b from bp 36 to bp 99, followed downstream by the sequence from bp 166 to bp 1433. Thus, this claim reads on the method for producing the approved product.

31. The method of claim 24 wherein said DNA sequence comprises a first nucleotide sequence joined to a second nucleotide sequence positioned downstream of said first sequence, said first and second sequences derived from cDNA clones of Factor VII, the joined sequences coding for a protein which upon activation has substantially the same biological activity for blood coagulation as Factor VIIa.

The expression construct encoding Factor VII currently used for production of the approved product comprises a segment of clone pVII565 (a Factor VII cDNA clone) joined to a segment of pVII2463 (also a Factor VII cDNA clone) downstream of the segment of clone pVII565. Thus, this claim reads on the method for producing the approved product.

32. The method of claim 24 wherein said DNA sequence comprises a first nucleotide sequence derived from a genomic clone of Factor VII, joined to a second nucleotide sequence positioned downstream of said first sequence, said second sequence derived from a cDNA clone of Factor VII, the joined sequences coding for a protein which upon activation has substantially the same biological activity for blood coagulation as Factor VIIa.

Any DNA sequence encoding human Factor VII will encode the approved product. Thus, this claim reads on a method for producing the approved product.

(10) The relevant dates and information pursuant to 35 U.S.C. § 156 (g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(a) Issue date of patent: November 15, 1988

(b) Effective Date of BB IND No. 2897 application: May 29, 1988

Date BB IND No. 2897 submitted: April 29, 1988

Date BB IND No. 2897 received by the FDA: April 29, 1988

(c) Date BLA No. 96-0597 (NOVOSEVEN) approved: March 25, 1999

(11) A brief description of the significant activities undertaken by the marketing applicant, Novo Nordisk, on behalf of the Applicant during the applicable regulatory review period with respect to the approved product, and the significant dates applicable to such activities, are set out in EXHIBIT 7.

(12) Applicant is of the opinion that U.S. Patent No. 4,784,950, is eligible for extension under 35 U.S.C. § 156 because it satisfies all the requirements for such an extension in as much as:

(i) the term of such patent has not expired before submission of this application (35 U.S.C. § 156(a)(1));

(ii) the term of such patent has never been extended (35 U.S.C. § 156(a)(2));

(iii) the application for extension is submitted by the owner of record, through undersigned counsel, in accordance with the requirements of 35 U.S.C. § 156(d);

(iv) the approved product, "NOVOSEVEN®" has been subject to a regulatory review period before its commercial marketing or use (35 U.S.C. § 156(a)(4));

(v) the permission for the commercial marketing or use of the product, "NOVOSEVEN®", after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of the Public Health Service Act under which such regulatory period occurred (35 U.S.C. § 156 (a)(5)(a)); and

(vi) no other patent has been extended for the same regulatory review period for the approved product (35 U.S.C. § 156(c)(4)).

Applicant requests an extension of the patent term of U.S. Patent No. 4,784,950 by 1,826 days (5 years) from the original expiration date of November 15, 2005, to November 15, 2010. This period of extension is calculated according to the following subsections of 37 C.F.R. § 1.775:

(a) The original expiration date of the Patent is 17 years from the date of issue, that is November 15, 2005.

(c) The length of the regulatory review period was 3,952 days, calculated as follows:

(1) The number of days from the effective date of original IND (BB) No. 2897 for the approved product, "NOVOSEVEN®" to the receipt by the FDA of the BLA (No. 96-0597), i.e., from May 29, 1988, to May 13, 1996 is 2,906 days.

(2) The number of days between initial submission of the BLA No. 96-0597 to the approval of the BLA, that is from May 13, 1996 to March 25, 1999, is 1,046 days.

(d) The term of the patent as extended from a human drug product is to November 15, 2010, that is an extension of 1,826 days, calculated according to 37 CFR § 1.778(d) as shown below.

(1) From the number of days of the regulatory review period calculated under subparagraph (c), the following are subtracted:

i) the period of time from the effective date of IND (BB) No. 2897 to the issuance of U.S. Patent No. 4,784,950 is 170 days, i.e., the period from April 29, 1988 to and including November 15, 1988 (U.S. Patent No. 4,784,950 issued before the filing of the BLA);

(ii) the number of days in the regulatory period as set forth in §1.775(c)(1) and §1.775(c)(2) during which the marketing applicants on behalf of the Applicant, did not act with due diligence, which is zero (0) days; and

(iii) One-half the number of days remaining in the period as set forth in §1.775(c)(1) after that period is reduced in accordance with paragraphs (d)(1)(i) and (ii), which is 1,368 days (2,906 - 170 = 2,736, 2,736 ÷ 2 = 1,368 days).

(2) Adding 2,414 days to the original expiration date of November 15, 2005, comes to May 25, 2012.

(3) Adding 14 years to the date of approval of the BLA comes to March 25, 2013.

(4) The earlier of the dates calculated under the subparagraphs (d)(2) and (3) above is May 25, 2012.

(5)(i) The original patent was issued after September 24, 1984. Adding 5 years to the original expiration date of the patent comes to November 15, 2010. The earlier of the dates calculated under the subparagraphs (d)(4) and (d)(5(i)) above is November 15, 2010.

(6) The original patent was not issued before September 24, 1984, so this paragraph is not applicable.

(13) Applicant, through its undersigned counsel, acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determinations to be made relative to the application for extension, in accordance with 37 C.F.R. § 1.765.

(14) A check in the amount of $1,120.00, payable to the Commissioner of Patents and Trademarks, is attached to cover the fee prescribed by 37 C.F.R. 1.20(j)(1) for receiving and acting upon this application for extension. If any additional fees are due, authorization is given to charge our deposit account number 03-1952, referencing docket no. 273802801500.

(15) Please direct all inquiries and correspondence relating to this application for patent term extension to:

Gladys H. Monroy

Morrison & Foerster
755 Page Mill Road
Palo Alto, CA 94304
Phone: (650) 813-5711
Fax: (650) 494-0792

(16) Submitted herewith is a certification that these application papers are being submitted in duplicate (EXHIBIT 8).

(17) Additionally submitted herewith is a Declaration of Gladys H. Monroy as patent counsel for Applicant pursuant to 37 CFR § 1.740 (b)(1) as authorized by the Power of Attorney executed by Applicant submitted herewith as EXHIBIT 9.

Respectfully submitted,

By: Gladys H. Monroy

Gladys H. Monroy
Registration No. 32,430

Morrison & Foerster
755 Page Mill Road
Palo Alto, CA 94304-1018
Direct: (650) 813-5711
Fax: (650) 494-0792

PTO/SB/96 (10-92)

CERTIFICATE UNDER 37 C.F.R. § 3.73(b)	Docket No.273802801500

In the application of:	Frederick S. Hagen et al.
Application No.:	06/810,002
Application Date:	December 16, 1986
Patent No.:	4,784,950
Date of Patent:	November 15, 1988
For:	EXPRESSION OF FACTOR VII ACTIVITY IN MAMMALIAN CELLS

ZymoGenetics, Inc., a a corporation organized under the laws of the state of Washington and having a place of business at 1201 Eastlake Avenue East, Seattle, WA 98101, certifies that it is the assignee of the entire right, title and interest in the patent application identified above by virtue of either:

A. ☒ An assignment from the inventors of the patent application identified above. The assignment was recorded in the Patent and Trademark Office on March 14, 1986, at Reel 4533, Frames 482-486, or for which a copy thereof is attached.

OR

B. ☐ A chain of title from the inventor(s) of the patent application identified above, to the current assignee as shown below:

☐ Additional documents in the chain of title are listed on a supplemental sheet.

☐ Copies of assignments or other documents in the chain of title are attached.

The undersigned has reviewed all the assignment documents identified above and, to the best of undersigned's knowledge and belief, title is in the assignee identified above.

The undersigned (whose title is supplied below) is empowered to sign this certificate on behalf of the assignee.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 14 May 1999

Debra K Leith

Name: Deb Leith
Title: Vice President of Intellectual Property and Business Development, Zymogenetics, Inc

ASSIGNMENT

WHEREAS, we, Frederick S. Hagen, Mark J. Murray, Sharon J. Busby, Kathleen L. Berkner, Margaret Y. Insley, Richard G. Woodbury and Charles L. Gray (hereinafter referred to as ASSIGNORS), having post office addresses of 3835-44th N.E., Seattle, Washington 98105; 2211-11th Avenue E., Seattle, Washington 98102; 4109 Meridian North, Seattle, Washington 98103; 3032-22nd Avenue West, Seattle, Washington 98199, 16860 N.E. 150th Street, Woodinville, Washington 98072, 15464-10th Avenue N.E., Seattle, Washington 98155, and 8014-41st Avenue N.E., Seattle, Washington 98115, respectively, have invented certain new and useful improvements in "EXPRESSION OF FACTOR VII AND IX ACTIVITIES IN MAMMALIAN CELLS," for which an application for United States letters patent was filed on December 16, 1985 and assigned Serial No. 810,002; and

WHEREAS, ZymoGenetics, Inc. (hereinafter referred to as ASSIGNEE), a corporation of the State of Delaware having a place of business at 2121 North 35th Street, Seattle, Washington 98103, is desirous of acquiring the entire right, title and interest in and to the invention and in and to any letters patent that may be granted therefor in the United States and in any and all foreign countries;

NOW, THEREFORE, in consideration of One Dollar ($1.00) and other good and valuable consideration, the receipt of which is hereby acknowledged, ASSIGNORS hereby sell, assign and transfer unto said ASSIGNEE the full and exclusive right, title and interest in and to said invention for the United States of America and its territorial possessions and all foreign countries, and the entire right, title and interest in and to any and all letters patent which may be granted therefor in the United States of America and its territorial possessions and in any and all foreign countries, and in any and all divisions, reissues and continuations thereof, including the right to claim priority rights deriving from said United States application by virtue of the International Convention, said invention,

application and all letters patent on such invention to be held and enjoyed by ASSIGNEE for its use and benefit and of its successors and assigns as fully and entirely as the same would have been held and enjoyed by ASSIGNORS had this assignment, transfer and sale not been made. ASSIGNORS hereby authorize and request the Commissioner of Patents and Trademarks to issue all letters patent on said invention to ASSIGNEE. ASSIGNORS agree to execute all instruments and documents required for the making and prosecution of applications for United States and foreign letters patent on said invention, for litigation regarding said letters patent, or for the purpose of protecting title to said invention or letters patent therefor.

3-5-86 — Frederick S. Hagen

Date — Frederick S. Hagen

STATE OF WASHINGTON)
) ss.
County of King)

On this 5th day of March, 1986, Frederick S. Hagen personally appeared before me and executed the foregoing document.

Notary Public in and for the
State of Washington,
residing in Seattle
My commission expires: 1/1/90

RECEL 4533 FRAME 483

3-5-86
Date

Mark J. Murray

STATE OF WASHINGTON)
) ss.
County of King)

On this 5th day of March, 1986, Mark J. Murray personally appeared before me and executed the foregoing document.

Notary Public in and for the
State of Washington,
residing in Seattle
My commission expires: 1/1/90

3.5.86
Date

Sharon J. Busby

STATE OF WASHINGTON)
) ss.
County of King)

On this 5th day of March, 1986, Sharon J. Busby personally appeared before me and executed the foregoing document.

Notary Public in and for the
State of Washington
residing in Seattle
My commission expires: 1/1/90

REEL 4533 FRAME 418

3/5/86
Date

K L Berkner
Kathleen L. Berkner

STATE OF WASHINGTON)
) ss.
County of King)

On this 5th day of March, 1986, Kathleen L. Berkner personally appeared before me and executed the foregoing document.

Notary Public in and for the
State of Washington,
residing in Seattle
My commission expires: 1/1/90

3/5/86.
Date

Margaret Y. Insley
Margaret Y. Insley

STATE OF WASHINGTON)
) ss.
County of King)

On this 5th day of March, 1986, Margaret Y. Insley personally appeared before me and executed the foregoing document.

Notary Public in and for the
State of Washington,
residing in Seattle
My commission expires: 1/1/90

REEL 533 FRAME 485

Feb 25, 1986
Date

Richard G. Woodbury
Richard G. Woodbury

STATE OF WASHINGTON)
) ss.
County of King)

On this 25 day of February, 1986, Richard G. Woodbury personally appeared before me and executed the foregoing document.

Hazel Forbes
Notary Public in and for the
State of Washington,
residing in Snohomish County
My commission expires: May 1989

March 5, 1986
Date

Charles L Gray
Charles L. Gray

STATE OF WASHINGTON)
) ss.
County of King)

On this 5th day of MARCH, 1986, Charles L. Gray personally appeared before me and executed the foregoing document.

Valery D. Stone
Notary Public in and for the
State of Washington,
residing in Seattle
My commission expires: 1/1/90

RECORDED
PATENT & TRADEMARK OFFICE
MAR 14 1986

REEL 4533 FRAME 486

PATENT
Docket No. 273802801500

CERTIFICATE OF MAILING BY "FIRST CLASS MAIL"

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on May __, 1999.

Kathy Johnston

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Hagen et al.

Serial No.: 08/810,002

Patent No.: 4,784,950

Filing Date: December 16, 1986

Issue Date: November 15, 1988

For: EXPRESSION OF FACTOR VII ACTIVITY IN MAMMALIAN CELLS

REVOCATION OF PRIOR POWER OF ATTORNEY AND POWER OF ATTORNEY AND PROSECUTION BY ASSIGNEE UNDER 37 C.F.R. § 3.71

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Zymogenetics, Inc., the assignee of the entire right, title and interest in this patent, hereby revoke all Powers of Attorney previously granted relating to this application and patent and appoint as its attorneys or agents, with full power of substitution, association, and revocation, to prosecute this application and to transact all business in the United States Patent and Trademark Office connected herewith:

Mani Adeli (Reg No. 39,585)
Erwin J. Basinski (Reg No. 34,773)
Sean Brennan (Reg No. 39,917)
Nicholas Buffinger (Reg No. 39,124)
Mark R. Carter (Reg No. 39,131)
Thomas E. Ciotti (Reg No. 21,013)
E. Victor Donahue (Reg No. 35,492)
Sean M. Fitzgerald (Reg No. 42,537)
Sanjay Bagade (Reg No. 42,280)
Frank P. Becking (Reg No. 42,309)
Barry E. Bretschneider (Reg No. 28,055)
Alan W. Cannon (Reg No. 34,977)
Robert K. Cerpa (Reg No. 39,933)
Raj S. Davé (Reg No. 42,465)
Stephen C. Durant (Reg No. 31,506)
Cheryl L. Franke (Reg No. 44,113)

Hector Gallegos (Reg No. 40,614)
Charles D. Holland (Reg No. 35,196)
Richard D. Jordan (Reg No. 33,519)
Ararat Kapouytian (Reg No. 40,044)
Antoinette F. Konski (Reg No. 34,202)
Susan K. Lehnhardt (Reg No. 33,943)
Wen Liu (Reg No. 32,822)
Harry J. Macey (Reg No. 32,818)
Gladys H. Monroy (Reg No. 32,430)
Dahna S. Pasternak (Reg No. 41,411)
William C. Revelos (Reg No. 42,101)
Debra A. Shetka (Reg No. 33,309)
E. Thomas Wheelock (Reg No. 28,825)
Karen K. Wong (Reg No. 44,409)
Douglas Hodder (Reg No. 41,840)
Madeline I. Johnston (Reg No. 36,174)
Cindy S. Kaplan (Reg No. 40,043)
Phanesh B. Koneru (Reg No. 40,053)
Jung-Hua Kuo (Reg No. 41,918)
Kawai Lau (Reg No. P-44,461)
David C. Lundmark (Reg No. 42,815)
Thomas D. Mays (Reg No. 34,524)
Kate H. Murashige (Reg No. 29,959)
Catherine M. Polizzi (Reg No. 40,130)
Robert Saltzberg (Reg No. 36,910)
Lee K. Tan (Reg No. 39,447)
Thomas G. Wiseman (Reg No. 35,046)
Frank Wu (Reg No. 41,386)

all of Morrison & Foerster LLP, 755 Page Mill Road, Palo Alto, California 94304-1018, telephone: (650) 813-5600, said appointment to be to the exclusion of the inventors and their attorneys in accordance with the provisions of 37 C.F.R. § 3.71 provided that if any one of said attorneys or agents ceases being affiliated with the law firm of Morrison & Foerster as partner, employee or of counsel, such attorney's or agent's appointment as attorney or agent and all powers derived therefrom shall terminate on the date such attorney or agent ceases being so affiliated.

Please direct all communications relative to this patent to:

Gladys H. Monroy
Morrison & Foerster LLP
755 Page Mill Road
Palo Alto, California 94304-1018

Please direct all telephone communications to Gladys H. Monroy at (650) 813-5711.

Zymogenetics, Inc.
a Washington corporation

Dated: May 14, 1999

Debra K. Leith

Name: Deb Leith
Title: Vice President of Intellectual Property and Business Development
Address: 1201 Eastlake Avenue East
Seattle, Washington 98102

UNITED STATES PATENT AND TRADEMARK OFFICE

In re. U.S. Patent No. 4,784,950
Issued: Nov. 15, 1988
To: Frederick S. Hagen, Mark J. Murray; Sharon J. Busby; Kathleen L. Berkner; Margaret Y. Insley; Richard G. Woodbury; and Charles L. Gray
For: EXPRESSION OF FACTOR VII ACTIVITY IN MAMMALIAN CELLS

Novo Nordisk A/S, hereby acknowledges that ZymoGenetics Inc., the patent owner of U.S. Patent number 4,784,950, is authorized to rely upon the marketing activities of Novo Nordisk A/S, the marketing applicant, in seeking the approval for commercial manufacture, use or sale of Coagulation Factor VIIa (recombinant), tradename NOVOSEVEN®, from the F.D.A. in the patent owners request for patent term extension.

Novo Nordisk A/S

By _____

Name: Karin Norvin Nilsson
Title: Manager, Corporate Patents

Date: 17 May 1999

pa-376431

UNITED STATES PATENT AND TRADEMARK OFFICE

In re. U.S. Patent No. 4,784,950
Issued: Nov. 15, 1988
To: Frederick S. Hagen, Mark J. Murray; Sharon J. Busby; Kathleen L. Berkner; Margaret Y. Insley; Richard G. Woodbury; and Charles L. Gray
For: EXPRESSION OF FACTOR VII ACTIVITY IN MAMMALIAN CELLS

Novo Nordisk N.A., a wholly owned subsidiary of Novo Nordisk A/S, hereby acknowledges that ZymoGenetics Inc., the patent owner of U.S. Patent number 4,784,950, is authorized to rely upon the marketing activities of Novo Nordisk A/S, the marketing applicant, in seeking the approval for commercial manufacture, use or sale of Coagulation Factor VIIa (recombinant), tradename NOVOSEVEN®, from the F.D.A. in the patent owners request for patent term extension.

Novo Nordisk N.A.

By _____

Name: STEVE T. ZELSON
Title: PRESIDENT

Date: 5/18/99

NOVOSEVEN® Coagulation Factor VIIa (Recombinant)

For Intravenous Use Only

DESCRIPTION

NovoSeven is recombinant human coagulation Factor VIIa (rFVIIa), intended for promoting hemostasis by activating the extrinsic pathway of the coagulation cascade.[1] NovoSeven is a vitamin K-dependent glycoprotein consisting of 406 amino acid residues (MW 50 K Dalton). NovoSeven is structurally similar to human plasma-derived Factor VIIa.

The gene for human Factor VII is cloned and expressed in baby hamster kidney cells (BHK cells). Recombinant FVII is secreted into the culture media (containing newborn calf serum) in its single-chain form and then proteolytically converted by autocatalysis to the active two-chain form. rFVIIa, during a chromatographic purification process. The purification process has been demonstrated to remove exogenous viruses (MuLV, SV40, Pox virus, Reovirus, BEV, IBR virus). No human serum or other proteins are used in the production or formulation of NovoSeven.

NovoSeven is supplied as a sterile, white lyophilized powder of rFVIIa in single-use vials. Each vial of lyophilized drug contains the following:

Contents	1.2 mg (60 KIU) Vial	4.0 mg (200 KIU) Vial
rFVIIa	1200 µg	4000 µg
sodium chloride*	5.84 mg	23.36 mg
calcium chloride dihydrate*	2.94 mg	11.76 mg
glycylglycine	2.64 mg	10.56 mg
polysorbate 80	0.14 mg	0.56 mg
mannitol	60.0 mg	240.0 mg

*per mg of rFVIIa: 0.44 mEq sodium, 0.06 mEq calcium

After reconstitution with the appropriate volume of **Sterile Water for Injection, USP (not supplied)**, each vial contains approximately 0.6 mg/mL NovoSeven (corresponding to 600 µg/mL). The reconstituted vials have a pH of approximately 5.5 in sodium chloride (3 mg/mL), calcium chloride dihydrate (1.5 mg/mL), glycylglycine (1.3 mg/mL), polysorbate 80 (0.1 mg/mL), and mannitol (30 mg/mL).

The reconstituted product is a clear colorless solution which contains no preservatives. NovoSeven contains trace amounts of proteins derived from the manufacturing and purification processes such as mouse IgG (maximum of 1.2 ng/mg), bovine IgG (maximum of 30 ng/mg), and protein from BHK-cells and media (maximum of 19 ng/mg).

CLINICAL PHARMACOLOGY

Pharmacodynamics

NovoSeven is recombinant Factor VIIa and, when complexed with tissue factor can activate coagulation Factor X to Factor Xa, as well as coagulation Factor IX to Factor IXa. Factor Xa, in complex with other factors, then converts prothrombin to thrombin, which leads to the formation of a hemostatic plug by converting fibrinogen to fibrin and thereby inducing local hemostasis.

Pharmacokinetics

Single-dose pharmacokinetics of NovoSeven (17.5, 35, and 70 µg/kg) exhibited dose-proportional behavior in 15 subjects with hemophilia A or B.[2] Factor VII clotting activities were measured in plasma drawn prior to and during a 24-hour period after NovoSeven administration. The median apparent volume of distribution at steady state was 103 mL/kg (range 78-139). Median clearance was 33 mL/kg/hr (range 27-49). The median residence time was 3.0 hours (range 2.4-3.3), and the $t_{1/2}$ was 2.3 hours (range 1.7-2.7). The median *in vivo* plasma recovery was 44% (30-71%).

CLINICAL STUDIES

Open Protocol Use

The largest number of patients who received NovoSeven during the investigational phase of product development were in an open protocol study[3,4,5] that began enrollment in 1988, shortly after the completion of the pharmacokinetic study. These patients included persons with hemophilia types A or B (with or without inhibitors), persons with acquired inhibitors to Factor VIII or Factor IX, and a few FVII deficient patients. The clinical situations were diverse and included muscle/joint bleeds, mucocutaneous bleeds, surgical prophylaxis, intracerebral bleeds, and other emergent situations. Dose schedules were suggested by Novo Nordisk, but they were subject to the option of the investigator. Clinical outcomes were not reported in a standardized manner. Therefore, the clinical data from the Open Protocol is problematic for the evaluation of the safety and efficacy of the product by statistical methods. The following two cases describe the extremes of the clinical outcomes that were observed under the Open Protocol:

Case #1: A one-year old hemophilia B patient had both an inhibitor to Factor IX and would experience severe anaphylactic reactions to any product containing Factor IX. His life threatening hypersensitivity reaction to Factor IX precluded the use of other coagulation products and NovoSeven was requested under the compassionate use program because it contained Factor VIIa and no other coagulation factors. Between the child's ages of one to three, he was successfully treated with NovoSeven for 23 spontaneous joint, muscle, and oral bleeds. NovoSeven was administered by intravenous bolus dosing at 90 µg/kg every two hours. Hemostasis was achieved each time within one to eight days therapy, without reported sequelae. Adverse events were infrequent, minor, and considered unrelated to NovoSeven treatment.

Case #2: A 36-year-old hemophilia A patient with long standing inhibitors experienced pain between his shoulderblades (DAY 0); he treated himself at home for three days with Anti-Inhibitor Coagulant Complex, Vapor Heated, FEIBA® VH IMMUNO. From DAY 16-DAY 18, the patient treated himself at home with Anti-Inhibitor Coagulant Complex, Heat Treated, Autoplex® T. On DAY 18, he awoke with paraparesis of the lower extremities and was hospitalized. A large epidural hematoma (C6 to T12) was seen on MRI. The following day (DAY 19), the patient began treatment with NovoSeven, 90 µg/kg every 2 (and later every 3) hours (DAY 19-36). Neurologic and symptomatic improvement was observed. On DAY 29, the NovoSeven dose interval was increased to every four hours. On DAY 31, the patient experienced a massive upper gastrointestinal bleed secondary to stress ulcers (likely decadron induced). He was hypotensive for over two hours, and by the next day, he was requiring large volumes of fluid support and developed abdominal pain. A laparotomy on DAY 32 revealed necrotic large bowel which required resection. Intraoperative and post operative hemostasis was satisfactory on NovoSeven and there was no evidence of thrombosis of the larger mesenteric vessels either at surgery or in the pathologic specimen. On the fourth day post-op (DAY 36), NovoSeven investigational supplies were depleted, and the patient began receiving Autoplex (72 U/kg every 6 hours) and four units of packed red cells per day. During Autoplex therapy, bleeding increased; there was coffee ground emesis in the naso-gastric tube. After two days (DAY 38), additional NovoSeven was provided, but the patient was then experiencing severe adult respiratory distress syndrome (ARDS). Within 24 hours of resuming NovoSeven treatment (DAY 40), the patient's life support was voluntarily removed. An autopsy noted the history of bleeding ulcer, ischemic colon, thrombocytopenia, diffuse hemorrhage, lung changes consistent with ARDS, history of epidural hemorrhage, arthropathy, and generalized edema. His

stomach had no signs of the ulcers seen the week before on endoscopy indicating healing. On gross neuropathologic exam, his epidural hematoma had resolved.

Dosing Study

A double-blind, randomized comparison trial[6] of two dose levels of NovoSeven in the treatment of joint, muscle and mucocutaneous hemorrhages was conducted in hemophilia A and B patients with and without inhibitors. Patients received NovoSeven as soon as they could be evaluated in the treatment centers (4 to 18 hours after experiencing a bleed). Thirty five patients were treated at the 35 µg/kg dose (59 joint, 15 muscle and 5 mucocutaneous bleeding episodes) and 43 patients were treated at the 70 µg/kg dose (85 joint and 14 muscle bleeding episodes).

Dosing was to be repeated at 2.5 hour intervals but ranged up to four hours for some patients. Efficacy was assessed at 12±2 hours or at end of treatment, whichever occurred first. Based on a subjective evaluation by the investigator, the respective efficacy rates for the 35 and 70 µg/kg groups were: excellent 59% and 60%, effective 12% and 11%, and partially effective 17% and 20%. The average number of injections required to achieve hemostasis was 2.8 and 3.2 for the 35 and 70 µg/kg groups, respectively.

One patient in the 35 µg/kg group and three in the 70 µg/kg group experienced serious adverse events that were not considered related to NovoSeven. Two unrelated deaths occurred; one patient died of AIDS and the other of intracranial hemorrhage secondary to trauma.

No direct comparisons to other coagulation products have been conducted, therefore no conclusions regarding the comparative safety or efficacy can be made.

INDICATIONS AND USAGE

NovoSeven is indicated for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX. NovoSeven should be administered to patients only under the direct supervision of a physician experienced in the treatment of hemophilia.

CONTRAINDICATIONS

NovoSeven Coagulation Factor VIIa (Recombinant) should not be administered to patients with known hypersensitivity to NovoSeven or any of the components of NovoSeven. NovoSeven is contraindicated in patients with known hypersensitivity to mouse, hamster, or bovine proteins.

WARNINGS

The extent of the risk of thrombotic adverse events after treatment with NovoSeven is not known, but is considered to be low. Patients with disseminated intravascular coagulation (DIC), advanced atherosclerotic disease, crush injury, or septicemia may have an increased risk of developing thrombotic events due to circulating TF or predisposing coagulopathy (See **ADVERSE REACTIONS**).

Additional data on the adverse event profile in general and regarding the frequency of thrombotic events in particular is being collected through a postmarket surveillance program. The NovoSeven Cooperative Registry surveillance program is designed to collect data on all uses of NovoSeven to expand the base of experience regarding the use of NovoSeven. All prescribers can obtain information regarding contribution of patient data to this program by calling 1-877-362-7355.

PRECAUTIONS

General

Patients who receive NovoSeven should be monitored if they develop signs or symptoms of activation of the coagulation system or thrombosis. When there is laboratory confirmation of intravascular coagulation or presence of clinical thrombosis, the rFVIIa dosage should be reduced or the treatment stopped, depending on the patient's symptoms.

Due to limited clinical studies which clearly address the effect of post-hemostatic dosing, precautions should be exercised when NovoSeven is used for prolonged dosing (See DOSAGE AND ADMINISTRATION section).

Information for Patients

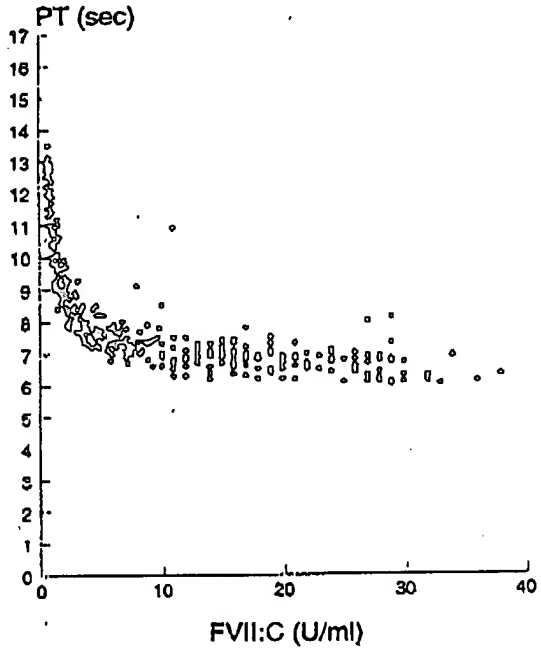
Patients receiving NovoSeven should be informed of the benefits and risks associated with treatment. Patients should be warned about the early signs of hypersensitivity reactions, including hives, urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.

Laboratory Tests

Laboratory coagulation parameters may be used as an adjunct to the clinical evaluation of hemostasis in monitoring the effectiveness and treatment schedule of NovoSeven although these parameters have shown no direct correlation to achieving hemostasis. Assays of prothrombin time (PT), activated partial thromboplastin time (aPTT), and plasma FVII clotting activity (FVII:C), may give different results with different reagents. Treatment with NovoSeven has been shown to produce the following characteristics:

PT: As shown below, in patients with hemophilia A/B with inhibitors, the PT shortened to about a 7-second plateau at a FVII:C level of approximately 5 U/mL. For FVII:C levels > 5 U/mL, there is no further change in PT.

PT versus FVII:C



aPTT: While administration of NovoSeven shortens the prolonged aPTT in hemophilia A/B patients with inhibitors, normalization has usually not been observed in doses shown to induce clinical improvement. Data indicate that clinical improvement was associated with a shortening of aPTT of 15 to 20 seconds.

FVIIa:C: FVIIa:C levels were measured two hours after NovoSeven administration of 35 µg/kg and 90 µg/kg following two days of dosing at two hour intervals. Average steady state levels were 11 and 28 U/mL for the two dose levels, respectively.

Drug Interactions
The risk of a potential interaction between NovoSeven and coagulation factor concentrates has not been adequately evaluated in preclinical or clinical studies. Simultaneous use of activated prothrombin complex concentrates or prothrombin complex concentrates should be avoided.

Although the specific drug interaction was not studied in a clinical trial, there have been more than 50 episodes of concomitant use of antifibrinolytic therapies (*i.e.*, tranexamic acid, aminocaproic acid) and NovoSeven.

NovoSeven should not be mixed with infusion solutions until clinical data are available to direct this use.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Two mutagenicity studies have given no indication of carcinogenic potential for NovoSeven. The clastogenic activity of NovoSeven was evaluated in both *in vitro* studies (*i.e.*, cultured human lymphocytes) and *in vivo* studies (*i.e.*, mouse micronucleus test). Neither of these studies indicated clastogenic activity of NovoSeven. Other gene mutation studies have not been performed with NovoSeven (*e.g.*, Ames test). No chronic carcinogenicity studies have been performed with NovoSeven.

A reproductive study in male and female rats at dose levels up to 3.0 mg/kg/day had no effect on mating performance, fertility, or litter characteristics.

Pregnancy
Pregnancy Category C. Treatment of rats and rabbits with NovoSeven in reproduction studies has been associated with mortality at doses up to 6 mg/kg and 5 mg/kg. At 6 mg/kg in rats, the abortion rate was 0 out of 25 litters; in rabbits at 5 mg/kg, the abortion rate was 2 out of 25 litters. Twenty three out of 25 female rats given 6 mg/kg of NovoSeven gave birth successfully, however, two of the 23 litters died during the early period of lactation. No evidence of teratogenicity was observed after dosing with NovoSeven. There are no adequate and well-controlled studies in pregnant women. NovoSeven should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The patients in whom NovoSeven is indicated are male.

Labor and Delivery
NovoSeven was administered to a FVII deficient patient (25 years of age, 66 kg) during a vaginal delivery (36 µg/kg) and during a tubal ligation (90 µg/kg). No adverse reactions were reported during labor, vaginal delivery, or the tubal ligation.

Nursing Mothers
It is not known whether NovoSeven is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
The safety and effectiveness of NovoSeven was not determined to be different in various age groups, from infants to adolescents (0 to 16 years of age). Clinical trials were conducted with dosing determined according to body weight and not according to age.

Geriatric Use
Clinical studies in hemophilia did not enroll geriatric patients.

ADVERSE REACTIONS
NovoSeven has been generally well tolerated in clinical studies in 298 patients with hemophilia A or B with inhibitors treated for 1,939 bleeding episodes. The table below lists adverse events that were reported in ≥2% of NovoSeven patients and were considered to be at le[illegible] possibly related or of unknown relationship to NovoSeven administration.

Body System Event	# of episodes reported (n=1,939 treatments)	# of unique patients (n=298 patients)
Body as a Whole		
Fever	16	13
Platelets, Bleeding, and Clotting		
Hemorrhage NOS	15	8
Fibrinogen plasma decreased	10	5
Skin and Musculoskeletal		
Hemarthrosis	14	6
Cardiovascular		
Hypertension	9	6

Events which were reported in 1% of patients and were considered to be at least possibly or of unknown relationship to NovoSeven administration were: allergic reaction, arthrosis, bradycardia, coagulation disorder, DIC, edema, fibrinolysis increased, headache, hypotension, injection site reaction, pain, pneumonia, prothrombin decreased, pruritus, purpura, rash, renal function abnormal, therapeutic response decreased, and vomiting.

In the 298 hemophilia patients, thrombosis was reported in two patients.

Serious adverse events that were probably or possibly related, or where the relationship to NovoSeven was not specified occurred in 14 of the 298 patients (4.7%). Six of these 14 patients died of the following conditions: worsening of chronic renal failure, anesthesia complications during proctoscopy, renal failure complicating a retroperitoneal bleed, ruptured abscess leading to sepsis and DIC, pneumonia, and splenic hematoma and GI bleeding.

OVERDOSAGE
Dose limiting toxicities of NovoSeven Coagulation Factor VIIa (Recombinant) have not been investigated in clinical trials. Two cases of accidental overdose by bolus administration have occurred in the clinical program. One hemophilia B patient (16 years of age, 68 kg) received a single dose of 352 µg/kg and one hemophilia A patient (2 years of age, 14.6 kg) received doses ranging from 246 µg/kg to 986 µg/kg on five consecutive days. There were no reported complications in either case. The recommended dose schedule should not be intentionally increased, even in the case of lack of effect, due to the absence of information on the additional risk that may be incurred.

DOSAGE AND ADMINISTRATION
Dosage
NovoSeven is intended for intravenous bolus administration only. Evaluation of hemostasis should be used to determine the effectiveness of NovoSeven and to provide a basis for modification of the NovoSeven treatment schedule; coagulation parameters do not necessarily correlate with or predict the effectiveness of NovoSeven.

The recommended dose of NovoSeven for hemophilia A or B patients with inhibitors is 90 µg/kg given every two hours until hemostasis is achieved, or until the treatment has been judged to be inadequate. Doses between 35 and 120 µg/kg have been used successfully in clinical trials, and both the dose and administration interval may be adjusted based on the severity of the bleeding and degree of hemostasis achieved.[7] The minimal effective dose has not been established. For patients treated for joint or muscle bleeds, a decision on outcome was reached for a majority of patients within eight doses although more doses were required for severe bleeds. A majority of patients who reported adverse experiences received more than twelve doses.

Post-Hemostatic Dosing: The appropriate duration of post-hemostatic dosing has not been studied. For severe bleeds, dosing should continue at 3-6 hour intervals after hemostasis is achieved, to maintain the hemostatic plug. The biological and clinical effects of prolonged elevated levels of Factor VIIa have not been studied; therefore, the duration of post-hemostatic dosing should be minimized, and patients should be appropriately monitored by a physician experienced in the treatment of hemophilia during this time period.

Reconstitution

Reconstitution should be performed using the following procedures.

1. Always use aseptic technique.
2. Bring NovoSeven (white, lyophilized powder) and the specified volume of Sterile Water for Injection, USP, (diluent) to room temperature, but not above 37°C (98.6°F).

   The specified volume of diluent corresponding to the amount of NovoSeven is as follows.

   1.2 mg (1200 µg) vial + 2.2 mL **Sterile Water for Injection, USP**
   4.8 mg (4800 µg) vial + 8.5 mL **Sterile Water for Injection, USP**

   After reconstitution with the specified volume of diluent, each vial contains approximately 0.6 mg/mL NovoSeven (600 µg/mL).
3. Remove caps from the NovoSeven vials to expose the central portion of the rubber stopper. Cleanse the rubber stoppers with an alcohol swab and allow to dry prior to use.
4. Draw back the plunger of a sterile syringe (attached to sterile needle) and admit air into the syringe.
5. Insert the needle of the syringe into the sterile water for injection vial. Inject air into the vial and withdraw the quantity required for reconstitution.
6. Insert the syringe needle containing the diluent into the NovoSeven vial through the center of the rubber stopper, aiming the needle against the side so that the stream of liquid runs down the vial wall (the NovoSeven vial does not contain a vacuum). **Do not inject the diluent directly on the NovoSeven powder.**
7. Gently swirl the vial until all the material is dissolved. The reconstituted solution is a clear, colorless solution which may be used up to 3 hours after reconstitution.

Administration

Administration should take place within 3 hours after reconstitution. Any unused solution should be discarded. Do not store reconstituted NovoSeven in syringes. NovoSeven is intended for intravenous bolus injection only and should not be mixed with infusion solutions. As with all parenteral drug products, reconstituted NovoSeven should be inspected visually for particulate matter and discoloration prior to administration. Do not use if particulate matter or discoloration is observed. Administration should be performed using the following procedures.

1. Always use aseptic technique.
2. Draw back the plunger of a sterile syringe (attached to sterile needle) and admit air into the syringe.
3. Insert needle into the vial of reconstituted NovoSeven. Inject air into the vial and then withdraw the appropriate amount of reconstituted NovoSeven into the syringe.
4. Remove and discard the needle from the syringe; attach a suitable intravenous injection needle and administer as a slow bolus injection over 2 to 5 minutes, depending on the dose administered.
5. Discard any unused reconstituted NovoSeven after 3 hours.

HOW SUPPLIED

NovoSeven Coagulation Factor VIIa (Recombinant) is supplied as a white, lyophilized powder in single-use vials, one vial per carton. The vials are made of Class I, Type I, hydrolytic, neutral, white glass, closed with a latex-free, bromobutyl rubber stopper, and sealed with an aluminum cap. The vials are equipped with a snap-off polypropylene cap. The amount of rFVIIa in milligrams and in micrograms is stated on the label as follows.

1.2 mg per vial (1200 µg/vial)	NDC 0169-7060-01
4.8 mg per vial (4800 µg/vial)	NDC 0169-7062-01

Storage

Prior to reconstitution, keep refrigerated (2-8°C /36-46°F). Avoid exposure to direct sunlight. Do not use past the expiration date.

After reconstitution, NovoSeven may be stored either at room temperature or refrigerated for up to 3 hours. Do not freeze reconstituted NovoSeven or store it in syringes.

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Rx only

U.S. Patent Nos. 4,382,083, 4,456,591, 4,479,938, and 5,180,583

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United States Patent [19]

Hagen et al.

[11] Patent Number: 4,784,950

[45] Date of Patent: Nov. 15, 1988

[54] EXPRESSION OF FACTOR VII ACTIVITY IN MAMMALIAN CELLS

[75] Inventors: Frederick S. Hagen; Mark J. Murray; Sharon J. Busby; Kathleen L. Berkner, all of Seattle; Margaret Y. Insley, Woodinville; Richard G. Woodbury; Charles L. Gray, both of Seattle, all of Wash.

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[21] Appl. No.: 810,002

[22] Filed: Dec. 16, 1986

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 724,311, Apr. 17, 1985.

[51] Int. Cl.[4] C12N 15/00; C12P 21/02; C07H 15/12; C07K 13/00

[52] U.S. Cl. 435/68; 435/172.3; 435/240.2; 435/320; 935/11; 935/32; 935/48; 935/60; 935/70; 536/27; 530/384

[58] Field of Search 536/27; 435/68, 172.3, 435/317, 240, 320; 530/384; 935/32, 47, 48, 55, 60, 70; 938/11

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1	4,784,950	183	900	----	06/810,002	11/15/88	12/16/85	04	NO	PAID

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ZY 83-23 USA 3B:C1 MAY'96

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STA
1	4,784,950	184	1990	----	06/810,002	11/15/88	12/16/85	08	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	9908.420CIP

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231

PTOL-439 (REV. 4-88)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 4,784,950
DATED : November 15, 1988
INVENTOR(S) : Frederick S. Hagen et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 31, line 35, delete "Botcham" and substitute therefor --Botchan--.
In column 32, line 23, delete "pD 3" and substitute therefor --pD3--.
In column 32, line 60, delete "7 ml" and substitute therefor --7ml--.
In column 33, line 8, delete "pUC 18" and substitute therefor --pUC18--.
In column 33, line 54, delete "Z40206" and substitute therefor --40206--.
In column 34, line 14, delete "pdX" and substitute therefor --pDX--.
In column 34, line 32, delete "7 ml" and substitute therefor --7ml--.
In column 34, line 35, delete "pCU12" and substitute therefor --pUC12--.
In column 34, line 53, after "expression" insert --of--.

Signed and Sealed this
Tenth Day of July, 1990

Harry F. Manbeck, Jr.

Attest:

Frances R. Marten

Attesting Officer

HARRY F. MANBECK, JR.
Commissioner of Patents and Trademarks

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 4,784,950

DATED : November 15, 1988

INVENTOR(S) : Frederick S. Hagen et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 21, line 63, delete "Hind II" and substitute therefor --Hind III--.

In column 22, line 1, delete "mm" and substitute therefor --mM--, line 59, delete "cDNa" and substitute therefor --cDNA--.

In column 24, line 13, delete "hybride" and substitute therefor --hybrid--.

In column 24, line 16, delete "cDNa" and substitute therefor --cDNA--.

In column 26, line 24, delete "BAM HI" and substitute therefor --Bam HI--.

In column 27, line 2, delete "BAM HI" and substitute therefor --Bam HI--.

In column 30, line 65, delete "BcL" and substitute therefor --Bcl--.

In column 31, line 33, delete "pBr 322" and substitute therefor --pBR322--, and delete "Botcham" and substitute therefor --Botchan--.

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 4,784,950
DATED : November 15, 1988
INVENTOR(S) : Frederick S. Hagen et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the abstract, column 2, line 3, after "Factor VII", insert --or Factor IX--.

In column 5, line 31, delete "usee" and substitute therefor --used--.

In column 5, line 52, delete "FVI1" and substitute therefor --FVII--.

In column 11, line 32, after "sequence was", delete "the" and substitute therefor --then--.

In column 13, line 38, delete "pUC 13" and substitute therefor --pUC13--.

In column 15, line 17, delete "terminal" and substitute therefor --termini--.

In column 17, line 56, delete "^{32}p" and substitute therefor --^{32}p--.

In column 18, line 65, delete "AC528" and substitute therefor --ZC528--.

In column 19, line 52, delete "Rb-enriched" and substitute therefor --Kb-enriched--.

NovoSeven®
BBIND 2897

DATE	CONTACT	DESCRIPTION
29 Apr 88	Submission	Original IND Submission.
31 May 88	Meeting	FDA Meeting: CMC issues, virus testing.
05 Jan 89	FDA Letter	Comments / questions from FDA based on review of IND.
07 Apr 89	FDA Letter	Review of 11/3/88 supplement & request for response to comments: testing of buffers, request for origina TEM photos, testing of monoclonal antibody producing cell line, find product release specifications, provide details of serum sources and testing.
08 May 89	Submission	Protocol Amendment: Response to FDA's January 5, 1989 letter. Revised Protocol: **USA/VII/001/KIN** (replacing **USA/FAC/001/VII**).
02 Aug 89	Submission	Response to FDA's April 7, 1989 letter.
05 Mar 90	Submission	Protocol Amendment: Revised protocol **USA/VII/006/DOS**
31 May 90	FDA Letter	FDA comments re: Protocol USA/VII/006/DOS
29 Nov 90	Submission	Response to FDA letter dated 5/31/90.
08 Mar 91	Submission	Protocol Amendment: New Protocol: USA/VII/008/THR.
26 Jul 91	Submission	Protocol Amendment: Revised protocol: USA/VII/008/THR
28 Oct 91	Meeting & Letter	Minutes for 10/28/91 meeting. Main purpose of meeting was to discuss with FDA Novo Nordisk's plans for submitting the PLA/ELA as soon as possible and obtain an expeditious review and approval for the enclosed limited indication.
09 Apr 92	Meeting	FDA Meeting to discuss process development

DATE	CONTACT	DESCRIPTION
20 Jul 92	Submission	Protocol Amendment: New Protocol: **USA/VII/012/KIN**
25 Mar 93	Submission	Pharmacology / Toxicology Information Amendment
28 Dec 93	Submission	New Compassionate Use Protocol
06 June 94	Meeting	FDA meeting to discuss manufacturing and clinical issues.
20 June 94	Submission	Meeting Minutes: June 6, 1994. Submission includes executive summary, presentations and discussions, list of attendees, presentation overheads.
20 Sept 94	Submission	Protocol Amendment: New Protocol (F7HT/USA/1/USA)
28 Dec 94	Submission	Information Amendment: Clinical. **Final report clinical study USA/VII/012/KIN** ".
23 Feb 95	Meeting	FDA Pre-ELA Meeting
02 Mar 95	Submission	Protocol Amendment: New Protocol. **F7HAEM/USA/2/USA**
20 Mar 95	Submission	Information Amendment: **Minutes of Pre-ELA Meeting**. Minutes of February 23, 1995 meeting held at FDA between representatives of the Div. of Establishment Licensing and Novo Nordisk (NNAS and NNPI).
09 Nov 95	Meeting	FDA Meeting at NIH to discuss clinical program.
01 Dec 95	Submission	Information Amendment: **Minutes of FDA Meeting** of November 9, 1995
09 Feb 96	Meeting	FDA Meeting with FDA Statisticians.
22 Feb 96	Submission	Information Amendment: **Minutes of FDA Meeting of February 9, 1996**
10 May 96	**PLA**	Submission of PLA

DATE OF CONTACT	CONTACT TYPE	DESCRIPTION
10 May 96	PLA	Submission of PLA (155 volumes, 3 copies, extra copies of summary volumes). SEE IND LOG FOR ACTIVITIES PRECEDING MAY 10, 96.
13 May 96	*FDA Letter*	Assignment of PLA reference # (96-0597) . The letter included where all future PLA correspondence should be directed.
19 June 96	*FDA Letter*	FDA notification that PLA is considered to be filed effective June 19, 96.
29 July 96	ELA	Submission of Establishment License Application (3 copies, six volumes) to Kathryn Zoon, Director, CBER.
3 September 96	*FDA Letter*	FDA notification that the PLA and ELA meet the definition of a specified biotechnology product for which an establishment license is no longer required. As a result, the PLA (5/10/96) and the ELA (7/29/96), have been combined into a biologics license application (BLA 96-0597) . Future correspondence should be directed to Jay Epstein.
26 September 96	Meeting	FDA/Blood Products Advisory Committee Meeting for rFVIIa.
4 November 96	Form FDA 482	Notice of Inspection, Gentofte, Denmark.
5 November 96	Form FDA 482	Notice of Inspection, Kalundborg, Denmark.
5 November 96	Submission	Final Study Report for Protocol F7HAEM/USA/3/USA (Surgery)
8 November 96	*FDA Form 483*	List of inspection observations at Kalundborg and Gentofte manufacturing facilities.
22 November 96	*FDA Letter*	Notification that amendment dated 11/6/96 is considered a major amendment and therefore an additional three months will be added to the BLA review clock. FDA letter dated 11/22/96.
3 December 96	Submission	Response to Form FDA 483 sent by NNAS.
18 March 97	Submission	Office of Establishment Licensing and Product Surveillance - follow-up to 483 responses
28 April 97	*FDA Letter*	Not approvable letter from the FDA received.
29 May 97	Meeting	CBER/Novo Nordisk Meeting to discuss BLA review
14 August 97	*FDA ROC*	FDA called Novo Nordisk regarding outcome of internal FDA meeting. FDA provided detailed list of information that must be submitted before a meeting can be scheduled.
10 September 97	Submission	BLA Amendment: Updated Integrated Summary of Efficacy, Benefit / Risk, and Statistics, in response to 4/28/97 FDA letter.

DATE OF CONTACT	CONTACT TYPE	DESCRIPTION
19 September 97	Submission	BLA Amendment - CMC response to 4/28/97 FDA letter.
3 October 97	Submission	BLA Amendment - Clinical response to 4/28/97 FDA letter.
20 Mar 98	***FDA Letter***	Letter from FDA regarding deficiencies in BLA.
17 Apr 98	Submission	Response to FDA letter of 3/20/98
23 June 98	***FDA Letter***	Questions from FDA's review committee meeting of June 22, 1998: 1 Regarding prospective validation; 2 regarding viral clearance; and 3 Regarding Novo's request to eliminate the spec for DNA testing in the bulk drug substance.
27 August 98	Meeting	Meeting with FDA to discuss progress of BLA review.
1 Sep 98	Submission	General Correspondence; Overheads from 8/27/98 FDA meeting and table of thrombotic adverse events from foreign, non-IND studies, as requested by FDA.
4 Sep 98	Submission	Process Validation Submission
28 Sep 98	***FDA FAX***	FDA faxed their comments on NovoSeven Package Insert.
13 Oct 98	NNPI ROC	Teleconference w/FDA to discuss Process Validation Deviation Reports
21 Oct 98	***FDA Letter***	FDA letter dated 10/20 received.
30 Oct 98	Meeting	Discussion of 10/20/98 letter and its resolution.
02 Nov 98	Meeting Minutes	Key Bullet Summary and Minutes of FDA Meeting of 10/30/98
12 Nov 98	Submission	Response to FDA Letter dated 10/20/98
24 Nov 98	***FDA FAX***	Letter from FDA acknowledging receipt of 11/12/98 response letter; and requesting information regarding: 1. For all batches manufactured from 11/98 - shut-down; 2. SOP info; 3. GMP Consultant's audit report.
3 Dec 98	NNPI ROC	Conference call held to discuss FDA Letter dated 11/24/98.
13 Jan 99	Submission	Response to FDA Request for Info letter dated 11/24/98.
25 Feb 99	ROC	Conference Call with FDA to communicate requests for clarification.
25 Feb 99	Submission	Response to FDA Request for Label Revision

DATE OF CONTACT	CONTACT TYPE	DESCRIPTION
15 Mar 99	Submission	Response to FDA Request for Info on stability data and patient tracking system.
25 Mar 99	FDA Letter	FDA approval letter for NovoSeven.

CERTIFICATION

The undersigned hereby certifies that this APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156, including EXHIBITS 1-8, is being submitted as duplicated originals.

May 21, 1999
Date

Gladys H. Monroy
Reg. No. 32,340

Application for Patent Extension
Patent No.: 4,784,950
Issued: November 15, 1988
Atty Docket No. 273802801500

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:	
Hagen et al.	
Application No.:	06/810,002
Application Date:	December 16, 1986
Patent No.:	4,784,950
Issued:	November 15, 1988
For:	EXPRESSION OF FACTOR VII ACTIVITY IN MAMMALIAN CELLS

DECLARATION

Commissioner for Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

Dear Sir:

The undersigned, as patent counsel for ZymoGenetics, Inc., the assignee of record of the above identified patent (herein after "Applicant"), hereby declares that:

(1) I am a registered patent attorney authorized to practice before the United States Patent and Trademark Office under Registration No. 32,430, and have general authority to act on behalf of the owner in connection with the APPLICATION FOR EXTENSION OF PATENT TERM UNDER § 156 submitted herewith for U.S. Patent No. 4,784,950.

(2) I have reviewed and understand the contents of the Application being submitted pursuant to 35 U.S.C. § 156 and 37 C.F.R. § 1.740.

(3) I believe the Patent is subject to extension pursuant to 35 U.S.C. § 156 and 37 C.F.R. §1.710.

(4) I believe an extension of the length claimed is justified under 35 U.S.C. § 156 and the applicable regulations.

(5) I believe the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. §1.720.

(6) I hereby declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of United States patent 4,845,075, issued July 4, 1989, and any extensions thereof.

May 21, 1999
Date

Gladys H. Monroy
Gladys H. Monroy
Reg. No. 32,430